## Remarks

This Reply is responsive to the Office Action dated April 20, 2006 and supplements the reply filed September 20, 2006. Claims 1-7, 15-19, 22, 27-32, 39, 48, 62, 63, 72-76 and 78-81 were pending in this application at the time of the Office Action dated April 20, 2006. As a result of this amendment, claims 1-74 have been canceled, claims 75, 78 and 79 have been amended, and new claims 82-98 have been added. Accordingly, claims 75, 76, 78, 79, and 82-98 are now pending and under examination.

A petition and fee for a one month extension of time are submitted herewith. Entry of the amendments and remarks submitted herein and reconsideration of the claimed subject matter pursuant to 37 CFR §1.112 is respectfully requested.

### Amendments to the Claims

The claims have been amended above to pursue the embodiment in independent claim 75, which is directed to methods of inhibiting gene expression *ex vivo* in a vertebrate cell using double stranded RNA corresponding to a target gene. As a result, claims 1-7, 15-19, 22, 27-32, 39, 48, 62, 63, 72-74 and 80-81 have been canceled. Cancellation of claims 1-7, 15-19, 22, 27-32, 39, 48, 62, 63, 72-74 and 80-81 is entered without prejudice to future prosecution, as Applicants intend to pursue these cancelled claims in a related application.

Claim 75 has been amended to indicate that at least one double stranded RNA may be delivered. Support for this amendment may be found at the very least in canceled claim 32. New claims 84-98 also find support in the canceled claims according to the following table. Claim 75 has also been amended to delete reference to delivery to the cell of the double stranded RNA as a single-stranded RNA that is purified in the absence of phenol or chloroform. These limitations have been re-submitted in new dependent claims 82 and 83. Claims 78 and 79 have been amended to depend on claim 75.

| New Claim | Corresponding Canceled Claim |
|---|---|
| 84 | 74 |
| 85 | 2 |
| 86 | 3 |
| 87 | 4 |
| 88 | 5 |
| 89 | 17 |
| 90 | 18 |
| 91 | 19 |
| 92 | 27 |
| 93 | 29 |
| 94 | 30 |
| 95 | 39 |
| 96 | 72 |
| 97 | 73 |
| 98 | 7 |

**Prior Art Rejections**

Claims 1-7, 15-19, 22, 28-32, 39, 62, 63, 72-76 and 78-81 were rejected under 35 U.S.C. §102(e) as being anticipated by Fire et al. (US 6,506,559). Applicants respectfully traverse the

rejection with respect to the amended claims above. In order to be anticipatory, it is well settled that a reference much teach every limitation of the claimed invention. At no point does Fire et al. disclose explanting a vertebrate cell from a vertebrate organism, supplying the cell with at least one double stranded RNA in an amount sufficient to specifically attenuate expression of the target gene, and implanting the cell into a vertebrate organism, wherein expression of the target gene is attenuated in the vertebrate cell. In fact, the inventors of US '559 have publicly stated that they did not believe that the invention would work in vertebrate cells.

For instance, the authors of Montgomery and Fire (Trends in Genetics (TIG), 1998, 14(7): 255-58) (attached), who are also two of the inventors of US '559, acknowledge that dsRNA "unleashes a vehement but somewhat non-specific response leading to general translational arrest" in mammalian cells. They postulate that "[a]ny gene-specific interference by dsRNA in PKR-proficient mammalian cells would be dependent on a transient lapse in the PKR response, or on a controlled level of dsRNA that was incapable of activating PKR," without disclosing how the PKR response would be quelled or what level of dsRNA would work (page 258, cols. 1-2).

Given that the Fire et al. specification includes no experiments in vertebrate cells, and the fact that the inventors themselves published that they did not believe that the methods would work in vertebrate cells without some control of the PKR response, it is difficult to see how US '559 discloses every limitation of the presently claimed invention. This is particularly true in light of the claims as currently amended, which require that gene expression in a vertebrate cell is actually attenuated.

Further, as Applicants argued in the reply filed September 20, 2006, Applicants believe that Fire et al. is not enabling prior art. Indeed, the Examiner herself has rejected Fire et al.'s claims to *ex vivo* inhibition of gene expression for lack of enablement in a continuation application of US '559 (copy of Office Action dated July 28, 2006 from Serial No. 10/283,190, copy attached). As stated therein, the Examiner asserts:

> The claimed invention is directed to methods of inhibiting gene expression in a cell in an animal by administering or synthesizing a double stranded RNA in a cell *ex vivo* followed by subsequent placement of the cell into a multicellular animal . . . The specification provides working examples of inhibition of gene expression by double stranded RNAs in *C. elegans* but provides no working examples of methods wherein double stranded RNA is provided to a cell *ex vivo* followed by subsequent transplantation. The specification also does not provide any concrete guidance on avoiding the problems associated with transplantation of cells . . . In the case of syngeneic cells, a skilled artisan would need to be taught what kind of cells would need to be isolated, how to isolate said cells, and how to culture said cells. This would need to be empirically determined. Thus, for the reasons described above with regard to cell transplantation, the specification as filed does not provide sufficient guidance, working examples and evidence as to how the skilled artisan would have made and used the claimed invention commensurate with the scope of the claims without undue experimentation. (USPTO Public PAIR, 10/283,190, Office Action, July 28, 2006, pp. 3-6)

Given that the Examiner herself refuses to grant the claimed subject matter to Fire et al. due to lack of enablement, Applicants fail to understand how Fire et al. can be considered to be enabling prior art against the current claims. According to the Federal Circuit, in order to enable, the prior art reference must teach one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation. *Minnesota Mining and Manufacturing Co, v. Chemque Inc.*, 64 USPQ2d 1270, 1278 (Fed. Cir. 2002); *see also Elan Pharmaceuticals Inc. v. Mayo Foundation for Medical Education and Research*, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003) ("The disclosure in an assertedly anticipating reference must be adequate to enable possession of the desired subject matter. It is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation."). If the Examiner herself has decided that the Fire et al. specification does not enable the skilled artisan to make and use the claimed invention absent undue experimentation, then Fire et al. US '559 should not be enabling prior art against the presently claimed invention.

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## Summary

This reply is fully responsive to the Office Action dated April 20, 2006. Therefore, a Notice of Allowance is next in order and is respectfully requested.

If the Examiner has any further questions relating to this Reply or to the application in general, she is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully submitted
By
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**Customer Number 26813**

October 16, 2006
Date

By: David L Provence
David L. Provence
Reg. No. 43,022
Direct Dial (612) 305-1005

CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that the Transmittal Letter and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 16 day of October, 2006, at 3:15 pm (Central Time).

By: Sandy Truehart
Name: Sandy Truehart

OCT 16 2006

UNITED STATES PATENT AND TRADEMARK OFFICE

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/283,190 | 10/30/2002 | Andrew Fire | 056100-5021-03 | 6388 |

9629 7590 07/28/2006

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
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| EXAMINER | |
|---|---|
| VIVLEMORE, TRACY ANN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

DATE MAILED: 07/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

| Office Action Summary | Application No. | Applicant(s) |
|---|---|---|
| | 10/283,190 | FIRE ET AL. |
| | Examiner | Art Unit |
| | Tracy Vivlemore | 1635 |



-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 April 2006*.

2a)☐ This action is FINAL. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *44,47,48,51,52,56,60,62,64,72,74,82,83,85,88,94,95 and 101-103* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *72,74,82,83,85,* is/are allowed.

6)☒ Claim(s) *44,47,48,51,52,56,88,94,95 and 101* is/are rejected.

7)☒ Claim(s) *60,62,64,102 and 103* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection not reiterated in this Action is withdrawn.

### *Claim Objections*

Claim 52 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 52 depends from claim 44, the scope of which is limited to worms and insects. Claim 52 however, recites that the target cell is a human cell at risk for infection by a virus. Therefore, claim 52 broadens, rather than narrows, the scope of claim 44.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 101 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 101 recites the limitation "said expression construct" in line 2. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51, 52, 56, 88, 94 and 95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

The claimed invention is directed to methods of inhibiting gene expression in a cell in an animal by administering or synthesizing a double stranded RNA in a cell *ex vivo* followed by subsequent placement of the cell into a multicellular animal. The claims encompass methods of inhibiting expression of any type of gene in any type of cell followed by transplantation of these cells into any organism for any purpose, including therapeutic purposes.

The specification describes inhibition of gene expression by administration of dsRNA. The specification states the disclosed methods can be performed in any type of organism and at page 12 lists some of these organisms. At page 15 the specification discloses that the method can be performed *ex vivo* with subsequent transplantation into an organism and contemplates a method of gene therapy. The specification provides working examples of inhibition of gene expression by double stranded RNAs in *C. elegans* but provides no working examples of methods wherein double stranded RNA is provided to a cell *ex vivo* followed by subsequent transplantation. The specification also does not provide any concrete guidance on avoiding the problems associated with transplantation of cells.

Post-filing art teaches that cell and organ transplantation is unpredictable, this unpredictability is exemplified in neuronal cells. Armstrong et al (Neuroscience, 2001, 106(1): 201-216) reported that histoincompatible allografts and neural xenografts are rejected within days or a few weeks with a vigor related to the degree of genetic disparity between donor and host, wherein the greater phylogenetic distance between donor and host, the more rapid and vigorous this rejection process. See page 201, in column 2.

Loseva et al (Brain Research, 2001, 915: 125-132) observed that xenografts of embryonic chicken brain were rapidly rejected from rat brain. See the abstract and throughout the entire document. These references clearly demonstrate the incompatibility and ultimate rejection of xenografts between donor and host species.

The unpredictability of cell transplantation of neuronal cells is generally applicable to other cell types. With regard to a xenogeneic or allogeneic transplant, one

major problem associated with these transplants is loss or rejection of the cell. The loss or rejection stems from an immune response to the foreign cell (see Platt 1998, page 11, 2nd col. under "The barriers to xenotransplantation"). While one might use drugs to immunosuppress a host, the specification does not teach what those drugs may be nor does the specification teach how to use such drugs in context of the instantly claimed methods of gene inhibition. In addition to this, a skilled artisan would need to know how to prevent infection of the host organism, while the host's immune system is suppressed (Platt, page 14, Box 1, 1st parag.). While use of syngeneic cells may circumvent the problem with cell rejection, Gage teaches that if long-term survival is required, success of the graft appears to depend on the cell type, the site of implantation and the type or class of promoter used (page 19, first column). Alternatively, in the cases that require a cell to integrate into a homotypic region and perform specific physiological roles, a skilled artisan would need to know the phenotype of the cell and the spatial location critical to its utility (e.g. a retinal cell transplant or a skin graft) (see Gage, page 19).

Thus, for reasons described above, a xenogenic or allogeneic transplant of cells faces the problem of host rejection. The methods involved to reduce the chance of rejection would need to be empirically determined. Coupled with this, to reduce rejection may involve methods of reducing infection in the host. This, too, would need to be empirically determined. In the case of syngeneic cells, a skilled artisan would need to be taught what kind of cells would need to be isolated, how to isolate said cells, and how to culture said cells. This would need to be empirically determined. Thus, for the reasons described above with regard to cell transplantation, the specification as filed does not provide sufficient guidance, working examples and evidence as to how the

skilled artisan would have made and used the claimed invention commensurate with the scope of the claims without undue experimentation.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless –**
>
> **(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.**

Claims 44, 47, 48 and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Wightman et al. (Cell 1993, vol. 75, pages 855-862) as evidenced by Grishok et al. (Cell 2001, vol. 106, pages 23-34).

The claimed invention is directed to a method of inhibiting gene expression in a cell in worms or insects by synthesizing within the cell a double stranded RNA that comprises a double stranded structure having a region identical to the target gene and a region complementary to the first region. The RNA can be transcribed from an expression construct, can be formed from a single self-complementary strand and the target cell can be at risk for infection by a pathogen.

Wightman et al. disclose that the lin-4 gene in *C. elegans* is a negative regulator of the lin-14 protein. Wightman et al. disclose that this regulation occurs post-transcriptionally and that the lin-4 RNA is complementary to portions of the lin-14 3'UTR and postulates that the regulation of lin-14 by lin-4 occurs through antisense base pairing to lin-14 mRNA. The lin-4 gene is expressed within a cell by the cell's

transcriptional machinery; because the instant specification does not provide an explicit definition of the term "expression construct", the transcriptional machinery of a cell is considered to meet the limitations of this term. As evidenced by the post-filing art of Grishok et al., lin-4 is expressed as an RNA of approximately 70 nucleotides that folds into structures containing double stranded regions. Grishok et al. further demonstrate that the RNAse III enzyme Dicer that processes dsRNAs to fragments of approximately 21 nucleotides is essential to the gene regulation mediated by lin-4, demonstrating that lin-4 forms a double stranded RNA that inhibits lin-14 expression.

Although Wightman et al. are silent as to the lin-4 gene regulating gene expression by forming a double stranded structure, the disclosure of Grishok et al. demonstrates that such a structure is formed. As stated in the MPEP (see MPEP 2112), something that is old does not become patentable upon the discovery of a new property. The claiming of an unknown property which is inherently present in the prior art does not necessarily make the claim patentable. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent in the prior art reference. This inherency argument is bolstered by *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67USPQ2d 1664, 1668 (Fed. Cir. 2003). Inherent anticipation does not require recognition in the prior art. Since Wightman et al. teach that lin-4 regulates expression of lin-14, and it has since been discovered that this gene forms a double stranded RNA structure, the teachings of Wightman et al. anticipate the instant invention. Furthermore, see *Eli Lilly & Co. v. Barr Labs., Inc., 251* F.3d 955, 970, 58 USPQ2d 1865 (Fed. Cir. 2001), "a limitation or the entire invention is inherent and in

the public domain if it is the "natural result flowing from" the explicit disclosure of the prior art".

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. (In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." (In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990)). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. (In re Best, 562 F.2d at 1255, 195 USPQ at 433).

***Claim Rejections - 35 USC § 103***

Claims 44, 47, 48 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al. (of record) in view of Noonberg et al. (of record).

The claimed invention is directed to a method of inhibiting gene expression in a cell in worms or insects by synthesizing within the cell a double stranded RNA that comprises a double stranded structure having a region identical to the target gene and a region complementary to this first region. The RNA can be transcribed from an expression construct, can be formed from a single self-complementary strand and the target cell can be at risk for infection by a pathogen.

Agrawal et al. teach self-stabilized oligonucleotides comprising a target hybridizing region and a self-complementary region. On page 15 Agrawal et al. teach that the self-complementary region of the oligonucleotide is fully or partially complementary to the hybridizing region while at page 9, line 30 through page 10 line 1 it is disclosed that the target hybridizing region is complementary to a nucleic acid sequence from a variety of sources including viruses, pathogens, cellular genes or gene transcripts. Pages 15 and 16 describe embodiments where the oligonucleotide is a single nucleic acid strand that forms a double stranded structure. On pages 17, line 27 through page 18 Agrawal et al. disclose that the self-stabilized oligonucleotides can be administered to the cells of an animal to inhibit gene expression in the animals. Routes of administration include oral and rectal. Agrawal et al. do not teach that their self-stabilized oligonucleotides are produced inside a cell through an expression construct.

Noonberg et al. teach oligonucleotide generators, expression constructs that allow high yield production of nucleic acids of defined size inside a cell for the purposes of gene regulation. Noonberg et al. further teach that delivery of nucleic acids via oligonucleotide generators circumvents the obstacles of extracellular degradation, cellular uptake, and intracellular sequestration.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the oligonucleotide generators taught by Noonberg et al. to produce the self-stabilized oligonucleotides taught by Agrawal et al. for inhibition of gene expression in a cell. Noonberg et al. provide a motivation to do, teaching that delivery of nucleic acids via oligonucleotide generators avoids the art-recognized problems of cellular uptake, degradation and intracellular sequestration. One of

ordinary skill in the art would have had a reasonable expectation of success in using the oligonucleotide generators of Noonberg et al. to produce self-stabilized oligonucleotides because Agrawal et al. taught that self-stabilized oligonucleotides can be used to inhibit gene expression and Noonberg et al. taught that nucleic acids useful in gene regulation can be produced in high yield using oligonucleotide generators.

Thus, the invention of claims 44, 47, 48 and 51 would have been obvious, as a whole, at the time of invention.

***Allowable Subject Matter***

Claims 72, 74, 82, 83 and 85 are free of the prior art searched.

Claims 49, 60, 62, 64, 102 and 103 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now

contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
July 21, 2006

PETER PARAS, JR.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Attorney Docket No. 56100-5021-03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE





In re Application of:

Inventors: Andrew Z. FIRE, et al.

Application No.: 10/283,190 Group Art Unit: 1635

Filed: October 30, 2002 Examiner: Vivlemore, T.A.

For: GENETIC INHIBITION OF DOUBLE-STRANDED RNA

## AMENDMENT AND RESPONSE

Commissioner of Patents and Trademarks
U.S. Patent and Trademark Office
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

In response to the Office Action dated December 27, 2005, please amend the above-referenced application as follows:

COPY

IN THE CLAIMS:

1. – 39. (canceled)

40. (canceled)

41. (canceled)

42. (canceled)

43. (canceled)

44. (currently amended): ~~The~~ A method ~~of claim 42~~ to inhibit expression of a target gene in a cell in a multicellular animal comprising providing at least one ribonucleic acid (RNA) to the cell in an amount sufficient to inhibit the expression of the target gene, wherein said RNA is provided to the cell by synthesizing said RNA in said cell, wherein the RNA comprises or forms a double-stranded structure containing a first strand consisting essentially of a ribonucleotide sequence which corresponds to a nucleotide sequence of the target gene and a second strand consisting essentially of a ribonucleotide sequence which is complementary to the nucleotide sequence of the target gene, wherein the first and the second ribonucleotide sequences are complementary sequences that hybridize to each other to form said double-stranded structure, and the RNA comprising the double-stranded structure inhibits expression of the target gene, and wherein said ~~invertebrate~~ animal is selected from the group consisting of nematodes, other worms, drosophila and other insects.

45. (canceled)

46. (canceled)

47. (currently amended): The method of claim ~~40~~ 44 wherein said RNA is transcribed from an expression construct.

48. (currently amended): The method of claim ~~40~~ 44 wherein said double-stranded structure is formed by a single self-complementary RNA strand containing said first and second ribonucleotide sequences.

49. (currently amended): The method of claim ~~40~~ 44 wherein the RNA is a double-stranded molecule containing two separate complementary RNA strands.

50. (canceled)

51. (currently amended): The method of claim ~~50~~ 44, claim 56 or claim 72 wherein said target cell is at risk for infection by a pathogen.

52. (currently amended): The method of claim ~~50~~ 44, claim 56 or claim 72 wherein said target cell is a human cell at risk for infection by a virus.

53. (canceled)

54. (canceled)

55. (canceled)

56. (currently amended): ~~The~~ A method ~~of claim 50~~ to inhibit expression of a target gene in a cell in an animal comprising providing at least one ribonucleic acid (RNA) to the cell in an amount sufficient to inhibit the expression of the target gene, wherein said RNA is provided to the cell by synthesizing said RNA in said cell, wherein the RNA comprises or forms a double-stranded structure containing a first strand consisting essentially of a ribonucleotide sequence which corresponds to a nucleotide sequence of the target gene and a second strand consisting essentially of a ribonucleotide sequence which is complementary to the nucleotide sequence of the target gene, wherein the first and the second ribonucleotide sequences are complementary sequences that hybridize to each other to form said double-stranded structure, and the RNA comprising the double-stranded structure inhibits expression of the target gene, wherein said

RNA is provided to said target cell ex vivo by introducing an expression construct that synthesizes said RNA in said cell and said cell is subsequently placed into said animal, and wherein the RNA is a double-stranded molecule containing two separate complementary RNA strands.

57. (canceled)

58. (canceled)

59. (canceled)

60. (previously presented): The method of claim 47 wherein said expression construct is directly injected into said animal in the vicinity of said target cell such that the construct is introduced into the target cell, thereby inhibiting expression of the target gene.

61. (canceled)

62. (previously presented): The method of claim 47 wherein said multicellular animal has a body cavity or interstitial space, and said expression construct is introduced into a body cavity or interstitial space of said animal such that the expression construct is introduced into the target cell, thereby inhibiting expression of the target gene.

63. (canceled)

64. (previously presented): The method of claim 47, wherein said multicellular animal has a digestive system, and wherein said expression construct is orally administered to said animal such that the expression construct is introduced into the target cell, thereby inhibiting expression of the target gene.

65. (canceled)

66. (canceled)

67. (canceled)

68. (cancel):

69. (cancel)

70. (cancel)

71. (cancel)

72. (currently amended): ~~The~~ A method ~~of claim 70~~ to inhibit expression of a target gene in a cell in an invertebrate animal comprising providing at least one ribonucleic acid (RNA) to the cell in an amount sufficient to inhibit the expression of the target gene, wherein said RNA is provided to the cell by synthesizing said RNA in said cell, wherein the RNA comprises or forms a double-stranded structure containing a first strand consisting essentially of a ribonucleotide sequence which corresponds to a nucleotide sequence of the target gene and a second strand consisting essentially of a ribonucleotide sequence which is complementary to the nucleotide sequence of the target gene, wherein the first and the second ribonucleotide sequences are complementary sequences that hybridize to each other to form said double-stranded structure and the RNA comprising the double-stranded structure inhibits expression of the target gene, and wherein the RNA is a double-stranded molecule containing two separate complementary RNA strands.

73. (canceled)

74. (currently amended): The method of claim ~~70~~ 72 wherein said RNA is provided to the cell by introducing an expression construct that synthesizes said RNA in said cell.

75. (canceled)

76. (canceled)

77. (canceled)

78. (canceled)

79. (canceled)

80. (canceled)

81. (canceled)

82. (previously presented): The method of claim 74 wherein said invertebrate animal has a digestive system, and wherein said expression construct is orally administered to said animal such that the expression construct is introduced into the target cell, thereby inhibiting expression of the target gene.

83. (currently amended): The method of claim ~~70~~ 72 wherein said invertebrate animal has a digestive system, and wherein the RNA is provided to said animal by feeding a second organism.

84. (canceled)

85. (previously presented): The method of claim 83 wherein said second organism is engineered to produce said RNA from an expression construct.

86. (canceled)

87. (canceled)

88. (currently amended): ~~The~~ A method ~~of claim~~ to inhibit expression of a target gene in a cell comprising providing at least one ribonucleic acid (RNA) to the cell in an amount sufficient to inhibit the expression of a target gene, wherein the RNA comprises or forms a double-stranded structure containing a first strand consisting essentially of a ribonucleotide sequence which corresponds to a nucleotide sequence of the target gene and a second strand consisting essentially of a ribonucleotide sequence which is complementary to the nucleotide sequence of the target gene, wherein the first and the second ribonucleotide sequences are complementary sequences that hybridize to each other to form said double-stranded structure, and the RNA comprising the double-stranded structure inhibits expression of the target gene, wherein said RNA is provided to the cell *ex vivo* by contacting said cell with said RNA and said cell is subsequently placed into an animal wherein the RNA is a double-stranded molecule containing two separate complementary RNA strands.

89. (canceled)

90. (canceled)

91. (canceled)

92. (canceled)

93. (canceled)

94. (currently amended): ~~The~~ A method ~~of claim 92~~ to inhibit expression of a target gene in a cell comprising providing at least one ribonucleic acid (RNA) to the cell in an amount sufficient to inhibit the expression of a target gene, wherein the RNA comprises or forms a double-stranded structure containing a first strand consisting essentially of a ribonucleotide sequence which corresponds to a nucleotide sequence of the target gene and a second strand consisting essentially of a ribonucleotide sequence which is complementary to the nucleotide sequence of the target gene, wherein the first and the second ribonucleotide sequences are complementary sequences that hybridize to each other to form said double-stranded structure, and the RNA

comprising the double-stranded structure inhibits expression of the target gene, wherein said RNA is provided to the cell *ex vivo* by introducing an expression construct that synthesizes said RNA in said cell and said cell is subsequently placed into an animal wherein the RNA is a double-stranded molecule containing two separate complementary RNA strands

95. (currently amended): The method of claim ~~92~~ 94 wherein said target cell is at risk for infection by a pathogen.

96. (canceled)

97. (canceled)

98. (canceled)

99. (canceled)

100. (canceled)

101. (new): The method of claim 44 wherein said invertebrate animal has a digestive system, and wherein said expression construct is orally administered to said animal such that the expression construct is introduced into the target cell, thereby inhibiting expression of the target gene.

102. (new): The method of claim 44 wherein said invertebrate animal has a digestive system, and wherein the RNA is provided to said animal by feeding a second organism.

103. (new): The method of claim 44 wherein said second organism is engineered to produce said RNA from an expression construct.

## REMARKS

Reconsideration of this application is requested.

With entry of this amendment, the claims in the case are claims 44, 47-49, 51, 52, 56, 60, 62, 64, 72, 74, 82, 83, 85, 88, 94, 95 and new claims 101-103. It is noted that, of these claims, claims 56, 88 and 94 were indicated to be allowable if presented in independent form; claims 44, 72, 83 and 85 were rejected only on double-patenting grounds; claims 51 and 52 were objected to or rejected essentially because of their dependence; and claims 47-49, 60, 62, 64, 74, 82, 83 and 95 are dependent from the claims indicated to be allowable or rejected only on double-patenting. Hence all of the claims are thought to be allowable. This includes new claims 101-103 which are drawn to the features of claims 82, 83 and 85 but depend from claim 44.

In essence, what the applicants have tried to do with the present amendment is to limit the claims to those which would appear on the record to be allowable, based on the nature of the Examiner's rejections and subject to the filing of a terminal disclaimer to obviate the double-patenting rejection. Other claims have been canceled but without accepting the Examiner's position thereon and without prejudice to the filing of one or more continuations directed thereto.

With respect to the pending claims, the applicants comment as follows on the issues raised by the Examiner:

Claim 44

This claim was rejected only for double-patenting based on applicants' U.S. 6,506,559. The terminal disclaimer filed herewith obviates this rejection.

Claims 47-49

These claims were rejected as not enabled. The applicants do not agree with the Examiner's rejection. However, for present purposes, claims 47-49 have been made dependent on claim 44 and should be allowable for the same reasons as claim 44.

Claims 51-52

These claims were included in an objection, based on their dependence, and in the Section 103(a) rejection. However, the amendments to claims 51 and 52 should obviate the objection and rejection of these claims.

Claim 56

This claim was indicated to be allowable if made independent. It has been so amended and should be allowable.

Claims 60, 62, 64

These claims depend from claim 47 and should be allowable for the reasons indicated above with respect to claim 47.

Claim 72

This claim was rejected only for double-patenting. The claim has been amended to be independent of claim 70 by incorporating therein the substance of claim 70, it being noted that claim 72 as amended refers broadly to invertebrate animals rather than reciting the Markush group of such animals as in claim 70. The broader language is thought to be warranted and, with the submission of the attached terminal disclaimer, claim 72 should be allowable.

Claims 74 and 82

Claim 74 has been made dependent on claim 72, which has been indicated to be allowable. Hence claim 74 should be allowable. The same is true for claim 82 which depends from claim 74. Claims 74 and 82 should be allowable for the same reasons as claim 72.

Claims 83 and 85

Same comments as made above for claims 74 and 82, i.e. claim 83 has been made dependent on claim 72 and claim 85 depends from claim 83. Claims 83 and 85 should be allowable for the same reasons as claim 72.

Claims 88 and 94

These claims were indicated to be allowable if presented in independent form. The claims have been appropriately amended so as to be independent by incorporating therein the substance of claim 87 and claim 92, respectively. Accordingly, claims 89 and 94 should be allowable.

Claim 95

This claim has been made dependent on claim 94 and should be allowable for the same reasons as claim 94.

Claims 101-103

These claims, as noted above, correspond with claims 82, 83 and 85, respectively, but depend from claim 44. Claims 101-103 are thought to be allowable for the same reasons as claim 44.

In view of the nature of the claim amendments, detailed discussion of the Examiner's various rejections is not considered warranted. However, the applicants wish to state on the record that they do not agree with or accept the Examiner's Section 112, 1st ¶ enablement rejection of claims 40-43, 45, 47-49, 57, 58, 60, 62, 64, 65 and 67-69. They also do not agree with or accept the Examiner's Section 102(b) and Section 103(a) rejections of the claims. The applicants have amended their claims herein for the purpose of obtaining early allowance of this application. However, they propose to contest the Examiner's rejections, insofar as they may be restated, in one or more separate continuation filings.

Consistent with the foregoing, the applicants request the Examiner to withdraw the double-patenting rejection based on applicants' U.S. Patent 6,506,559 in view of the attached Terminal Disclaimer.

As for the other issues raised by the Examiner, the claims rejected as not enabled, as noted, have been canceled, except as otherwise indicated, without prejudice. Hence reconsideration of the Section 112, 1st ¶ rejection as set out on pages 2-4 of the action is requested.

The Section 112, 2nd ¶ rejection and the claim objections as set out on pages 5-6 have been obviated by the cancellation, without prejudice, of claims 41-43, 45, 50-52, 55, 65 and 67-69.

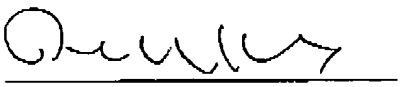
The Examiner's Section 102(b) and Section 103(a) rejections are not applicable, by the Examiner's acknowledgement, to the claims as amended herein. Hence reconsideration of the Section 102(b) and Section 103(a) rejections is requested.

Favorable action is requested.

Respectfully submitted

Dated: April 27, 2006

**Morgan, Lewis & Bocklus LLP**



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